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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/728,291	12/04/2003	Stephen F. Badylak	3220-73986	7088

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EXAMINER	
FORD, ALLISON M	

ART UNIT	PAPER NUMBER
1651	

NOTIFICATION DATE	DELIVERY MODE
09/23/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

indocket@btlaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/728,291	BADYLAK ET AL.	
	Examiner	Art Unit	
	ALLISON M. FORD	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 June 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-16 and 25-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-16 and 25-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20100917*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/18/2010 has been entered.

Claims 1-8 and 17-24 have been cancelled, new claims 25-34 have been added. Claims 9-16 and 25-34 are currently pending in the current application, all of which have been considered on the merits.

Response to Arguments

Applicants' response of 6/18/2010 has been fully considered. Rejections/objections not repeated herein have been withdrawn. Applicants' traversals of maintained rejections/objections are addressed below, as appropriate.

Initially, Applicants have requested clarification as to whether or not Bissell et al, made of record with the advisory action mailed 3/11/2010, was being relied upon for the rejection of claims 9-16 under 35 USC 103(a) maintained in the Advisory Action. In response, it is submitted that Bissell et al was cited to further evidence the Examiner's position that it was well known in the art that hepatocytes could be cultured *in vitro* in conditions in which they will retain their functionality, however the rejection of record was not being modified to further rely on Bissell et al, the rejection over Badylak et al and Saad et al was complete on its own.

With regards to the rejection of claims 9-16 as being obvious under 35 USC 103(a), Applicants have continued to traverse on the grounds that the Examiner has not established a *prima facie* case of obviousness. Specifically, Applicants assert that the mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art, citing *KSR International Co. v. Teleflex Inc,* 82 USPQ2d 1385, 1396 (2007). Applicants maintain that the Examiner has not provided sufficient evidence that one having ordinary skill in the art would have had a reasonable expectation that one could have successfully cultured hepatocytes in a manner in which they would retain their functionality (as defined by the instant claims) on liver basement membrane, as suggested by Badylak et al.

Applicants further assert that Saad et al not only does not support the assertion that hepatocytes would have been expected to maintain their functionality, but actually teaches against such an expectation, as Saad et al teach that cultures comprising ECM components are problematic for maintaining the expression of liver-specific functions in hepatocyte cultures, and Saad et al teach that it is the liver cell components in the crude liver membrane fraction (used by Saad et al) that are responsible for supporting hepatocyte function in vitro.

Applicants further assert that the instant invention yields unexpected results, specifically that that the current method provides the unexpected result of being capable of maintaining functional hepatocytes in culture, whereas the prior art (evidenced by Saad et al) teach such a task was difficult, at best, and assert Saad et al actually teach away from such, as discussed above.

Applicants' arguments have been fully considered, but remain unpersuasive. Regarding the argument that the Examiner has not established a *prima facie* case of obviousness because there was not sufficient evidence that one would have had a reasonable expectation that hepatocytes cultured on liver basement membrane would retain their functionality (as defined by the claims), it is submitted that the legal standard for obviousness does not require absolute predictability, but only at least some degree of

predictability to provide a reasonable expectation of success, see *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). In the instant case it is being asserted that hepatocytes seeded onto liver basement membrane *in vitro* would be reasonably expected to exhibit the same cellular functions as hepatocytes exhibit *in vivo*. This assertion is based on the fact that *in vivo* functional hepatocytes are attached to the same liver basement membrane (i.e. basal lamina); therefore the same cells are being re-seeded onto the same substrate *in vitro* on which they are known to be functional *in vivo*. While it is acknowledged that the art recognized that hepatocytes lost functionality *in vitro* when cultured on single protein substrates (i.e. substrate consisting of single layers of collagen type I or type IV, substrate consisting of laminin, or substrates consisting of fibronectin (See Bissell et al & Saad et al)), liver basement membrane is not a single protein substrate, but rather the complex combination of extracellular structure which naturally supports hepatocyte growth and function *in vivo*. It is agreed that one having ordinary skill in the art would not have had a reasonable expectation of successfully culturing hepatocytes in a manner in which they would retain their functionality (as defined by the instant claims) on a substrate consisting of any one or two extracellular matrix components, as the art clearly showed that individual proteins were insufficient to support maintenance of hepato-cellular function; however, it is respectfully submitted that Applicants have provided no evidence that there would have been no reasonable expectation of successfully culturing hepatocytes such that they maintain their functionality (as defined by the claims) on liver basement membrane, which is their natural substrate *in vivo*.

In response to Applicants' argument of unexpected results, it is respectfully submitted that it is not unexpected that the natural hepatocyte substrate (liver basal lamina/basement membrane) which is responsible for maintaining hepatocyte functionality *in vivo* is also capable of maintaining hepatocyte functionality *in vitro*. The results presented in the specification have been reconsidered, and while it is agreed that the liver basement membrane produced greater albumin production per cell than the double collagen gel assay (i.e. the art recognized technique for maintaining hepato-cellular function *in vitro*), this

cannot be considered evidence of unexpected results, because one having ordinary skill in the art would have expected liver basement membrane (the natural substrate of hepatocytes) to be superior to a single protein substrate, based on the teachings in the art (i.e. Bissell et al, Saad et al) that substrates consisting of single proteins were incapable of supporting hepato-cellular function.

The rejection of record has been modified to delete reference to Saad et al, as it is believed that the teachings of Badylak et al (in either reference) are sufficient on their own to support a *prima facie* case of obviousness.

With regards to the non-statutory double patenting rejection of claims 9-16 over claims U.S. Patent No. 6,793,939, and of claims 1, 3, 12 and 14 of U.S. Patent No. 7,482,025, each in view of Badylak (WO 98/25637), each in view of Saad et al, Applicants have reiterated their arguments presented against the rejection under the statute of 35 USC 103(a).

In response, for the same reasons as discussed above, the rejections have been modified to delete reliance on Saad et al, as the teachings of Badylak et al are considered to be sufficient to support the obviousness-type double patenting rejections.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 9-16 and 26-33 are rejected under 35 U.S.C. 103(a) as being obvious over each of Badylak WO 98/25637 and Badylak US Patent 6,793,939 (national stage entry of PCT/US97/22727).

It is noted the applied **patent** reference (US 6,793,939) has a common inventor and assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2). Please note the WIPO publication is prior art under 35 USC 102(b) and cannot be overcome in such a manner.

In each reference Badylak disclose methods of inducing endogenous tissue formation at a site in need thereof by administering a graft composition comprising liver basement membrane in an amount effective to induce the repair of the tissue at the site of administration. Badylak disclose the graft composition can be administered as a multi-layered composition formed from two or more layers of liver basement membrane (See WO 98/25637 Pgs 8-9/ See USP '939 col. 6, ln 13-64). The thickness of individual layers/sheets would be routinely optimized to suit the intended implantation site's needs (size and shape). Badylak further state the basement membrane can be provided in various forms, including a fluidized liquid (which can also be considered a gel) or powder form (See WO 98/25637 Pg. 4-5/ See USP '939 col. 3, ln 45-col. 4, ln 11).

Badylak further disclose eukaryotic cells may be seeded onto the liver basement membrane prior to implantation to enhance the tissue replacement capabilities of the graft material upon administration.

Cells corresponding to the target tissue site (target tissue site being the site to which the graft is being administered to induce endogenous tissue formation) may be cultured on the liver basement membrane material, and the graft then implanted to the corresponding target tissue site. For example, Badylak discloses culturing keratinocytes on liver basement membrane for use as a skin graft, or culturing endothelial cells on liver basement membrane for use as a vascular graft. Badylak further discloses other cell types, including hepatocytes, may be cultured on the liver basement membrane (See WO 98/25637 Pg 12/ See USP '939 col. 8, ln 30-col. 9, ln 23).

Badylak differs from the instant method in that, while he suggests producing a graft material comprising liver basement membrane with hepatocytes cultured thereupon, he does not disclose administering such a graft for use as a liver tissue graft to repair damaged or diseased liver tissue. Badylak further differs in that he does not report on the functionality of the hepatocytes once cultured on the liver basement membrane.

However, at the time the invention was made the need for a method of repairing damaged or diseased liver tissue was well recognized, and thus the artisan of ordinary skill would have been motivated to adapt the method of Badylak to select hepatocytes as the tissue-specific eukaryotic cell to be seeded upon the liver basement membrane, and then subsequently administer the hepatocyte-containing liver basement membrane graft composition to liver of a patient in need thereof in order to induce repair of the damaged or diseased liver, thereby solving the recognized need in the art. One would have had a reasonable expectation of successfully implanting the graft material suggested by Badylak (hepatocyte-containing liver basement membrane graft composition) for the repair of damaged or diseased liver tissue because Badylak teaches tissues produced with the liver basement membrane can be implanted to repair damaged or diseased tissues in vitro by selecting the appropriate endogenous cell type for production of the graft.

With regards to the ability of the hepatocytes to maintain their functionality (as defined by the instant claims) upon seeding onto the liver basement membrane: while it is understood that hepatocytes can quickly loss their functionality during *in vitro* culture on simple substrates (i.e. single layer collagen gels), unlike simple substrates consisting of a single extracellular protein, liver basement membrane is the actual extracellular matrix complex which supports hepato-cellular functions (including albumin production, urea production and cytochrome p450 production) *in vivo*; thus one having ordinary skill in the art would have had a reasonable expectation that hepatocytes seeded onto liver basement membrane *in vitro* would exhibit the same functionality as hepatocytes provided on the same liver basement membrane *in vivo*. It was known in the art that the substrate on which hepatocytes are cultured has a strong effect on the maintenance of hepato-cellular functions, yet, because liver basement membrane is the same substrate which hepatocytes naturally grow on *in vivo*, one would have had a reasonable expectation that the liver basement membrane of Badylak would be sufficient to support normal hepato-cellular functions *in vitro*, as well. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 9-16 and 25-34 are rejected under 35 U.S.C. 103(a) as being obvious over each of Badylak WO 98/25637 and Badylak US Patent 6,793,939 (national stage entry of PCT/US97/22727), in view of Daddona et al (WO 89/03885).

The teachings of each Badylak reference are set forth above. The teachings are held to render obvious the method of claims 9-16 and 26-33. The method of Badylak references, however, differ from the method of instant claims 25 and 34, each of which require removal of endotoxins from the liver basement membrane prior to seeding the hepatocytes on the liver basement membrane.

However, at the time the invention was made it was well known in the art that endotoxins can have detrimental effects if included in pharmaceutical compositions or biological preparations intended for administration to man, including induction of pyrogenic and/or shock reactions (See Dadonna et al,

Pg. 1, lines 1-6); thus there was a recognized need to remove endotoxins from any composition intended for introduction into man.

The liver basement membrane of Badylak is intended for introduction into a human for the purpose of restoring damaged or defective tissues, thus based on the recognized need in the art to remove endotoxins from biological material intended for introduction into man, one having ordinary skill in the art would have been motivated to remove endotoxins from the liver basement membrane of Badylak.

Dadonna et al disclose methods of removing endotoxins from proteinaceous biological material by use of non-denaturing detergents, such as bile salts, such as taurodeoxycholate (See Dadonna et al, Pg. 3, ln 5- Pg. 4, ln 9). The non-denaturing detergent can be applied to the biological material in combination with chelating agents for removal of divalent cations from the biological material (See Dadonna et al, Pg. 4, ln 6-9). The method of Dadonna et al results in substantial removal of endotoxin contaminants without denaturing the protein of the biological material.

It is submitted that one would have found it *prima facie* obvious to apply the method of Dadonna et al to the liver basement membrane of Badylak in order to remove endotoxins from the liver basement membrane so as to avoid the potential immunologic response of said endotoxins upon implantation. Noting that the method of Badylak does involve a step of cleaning the liver basement membrane, including treatment with a non-denaturing detergent and EDTA (See WO 98/25637 paragraph spanning Pgs 3-4/See USP '939 col. 3, ln 5-21), one would have had a reasonable expectation of successfully incorporating the bile salt detergent of Dadonna et al as the non-denaturing in the method of Badylak to effectively remove endotoxins from the liver basement membrane prior to seeding of any cells. Therefore the invention as a whole would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise

extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 9-16 and 26-33 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 6,793,939, in view of Badylak (WO 98/25637).

The patented claims disclose methods of inducing the formation of endogenous tissue at a site in need thereof by implanting a graft composition comprising the same liver basement membrane as disclosed in the current claims; the patented claims differ in that they do not specify the liver as the endogenous tissue in need of repair, and they do not disclose hepatocytes being present on the liver basement membrane.

However, Badylak (WO 98/25637), which discloses the same liver basement membrane material for implantation to repair damaged tissue, disclose eukaryotic cells may be seeded onto the liver basement membrane prior to implantation to enhance the tissue replacement capabilities of the graft material upon administration. Badylak discloses hepatocytes amongst the cells that may be cultured on the liver basement membrane (See WO 98/25637 Pg 12). Considering that liver basement membrane is the natural substrate for hepatocytes *in vivo*, one would have had a reasonable expectation that the same liver basement membrane would be capable of supporting hepato-cellular functions (including those currently claimed) *in vitro*, as well.

Therefore, though the current claims and the patented claims are not identical, they are not considered patentably distinct, because it would have been obvious to one of ordinary skill in the art to improve upon the patented method by including tissue-specific cells on the liver basement membrane material, as suggested by Badylak. The effect of the liver basement membrane on the hepatocytes, specifically supporting retention of liver specific activity of the cells would have been expected based on the fact that liver basement membrane is the natural substrate for hepatocytes *in vivo*.

Claims 9, 12, 26 and 29 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 12 and 14 of U.S. Patent No. 7,482,025, in view of Badylak (WO 98/25637).

The patented claims disclose methods of inducing the formation of endogenous tissue at a site in need thereof by implanting a graft composition comprising the same gelled liver basement membrane as disclosed in the current claims, and with endogenous cells cultured thereupon; the patented claims differ in that they do not specify the liver as the endogenous tissue in need of repair, and they do not disclose hepatocytes as the specific cell type cultured thereupon.

However, Badylak (WO 98/25637), which discloses the same liver basement membrane material for implantation to repair damaged tissue, disclose eukaryotic cells may be seeded onto the liver basement membrane prior to implantation to enhance the tissue replacement capabilities of the graft material upon administration. Badylak discloses hepatocytes amongst the cells that may be cultured on the liver basement membrane (See WO 98/25637 Pg 12). Considering that liver basement membrane is the natural substrate for hepatocytes *in vivo*, one would have had a reasonable expectation that the same liver basement membrane would be capable of supporting hepato-cellular functions (including those currently claimed) *in vitro*, as well.

Therefore, though the current claims and the patented claims are not identical, they are not considered patentably distinct, because it would have been obvious to one of ordinary skill in the art to

improve upon the patented method by including tissue-specific cells on the liver basement membrane material, as suggested by Badylak. The effect of the liver basement membrane on the hepatocytes, specifically supporting retention of liver specific activity of the cells would have been expected based on the fact that liver basement membrane is the natural substrate for hepatocytes *in vivo*.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALLISON M. FORD whose telephone number is (571)272-2936. The examiner can normally be reached on 8:00-6 M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Allison M. Ford/
Primary Examiner, Art Unit 1651